REMARKS

Claims 1, 2, 4-6, 9-16, 18, 19 and 25-30 are pending in the subject application. The Examiner has withdrawn claims 1-2, 4-6, 9-16, 18, 25, 26 and 30. Applicants respectfully note that the Examiner has erroneously withdrawn claim 30 from consideration. In response to a July 8, 2004 Restriction Requirement issued in connection with the subject application, applicants elected Group II, i.e. claims 19, 27, 28 and 30, for examination. Accordingly, claim 29 should be withdrawn and claim 30 should be pending and under examination. Applicants have cancelled withdrawn claims 1, 2, 4-6, 9-16, 18, 25 and 26.

Applicants have also hereinabove cancelled claim 27 without prejudice or disclaimer to their right to pursue the subject matter of this claim in this or a future application. In addition, applicants have hereinabove amended claim 19. Support for this amendment may be found inter alia in the specification at page 92, lines 1-3; page 103, lines 8-9; and cancelled claim 27. The remaining changes to the claims introduce minor format changes. Applicants have also amended page 11, lines 17-18. Support for this amendment may be found inter alia in the specification at page 56, lines 24-26. Applicants maintain that these amendments do not involve any issue of new matter. Therefore, entry of these amendments is respectfully requested such that claims 19, 28 and 30 will be pending and under examination.

Objections to the Specification

The Examiner stated that the specification should be amended on page 1 to reflect the status of the parent application.

In response, applicants note that parent application, U.S. Serial No. 09/329,917, is pending as currently reflected in the subject application.

The Examiner stated that although the specification has a section for the Brief Description of the Figures and Figures 9A-9F are mentioned, there is no description of these figures.

In response, applicants have hereinabove amended page 11 of the specification to include a description for Figures 9A-9F.

In view of the above remarks, applicants respectfully request that the Examiner reconsider and withdraw these grounds of objection.

Claim Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 19 and 27-29 under 35 U.S.C. §112, first paragraph. The Examiner concedes that the specification is enabling for a method of treating prostate cancer in a subject in need of such treatment wherein said prostate cancer overexpresses HER-2/neu comprising the step of administering a humanized antibody against the extracellular domain of HER-2/neu or a human monoclonal antibody against the extracellular domain of HER-2/neu. However, the Examiner asserts that it does not reasonably provide enablement for a method of treating prostate cancer in an individual in need of such treatment comprising the step of administering an antibody to HER-2/neu. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected to make and use the invention commensurate in scope with these

claims.

The Examiner stated that the claims are drawn to a method of treating prostate cancer in a subject in need of such treatment comprising the step of administering an antibody to HER-2/neu, which includes treating with (1) any antibody to HER-2/neu regardless of where it binds on HER-2/neu, (2) regardless of whether it cross reacts with other antigens including EGFR receptor, (3) regardless of whether the antibody is monoclonal or polyclonal, (4) regardless of whether the antibody is humanized for treatment of a human subject as contemplated, (5) regardless of whether or not cancer cells express HER-2/neu and (6) regardless of the extent of expression of HER-2/neu.

The Examiner also stated that the specification teaches the immunohistochemically identified membrane overexpression of HER-2/neu in primary prostate cancer samples (citing pages 87-96 of the specification).

The Examiner asserted that one cannot extrapolate the teaching of the specification to the scope of the claims for the following reasons.

Allegedly, although Agus et al., whose authors include the instant inventors, teach a successful method of treating prostate cancer in a subject comprising administering to the subject a therapeutically effective amount of Herceptin which is a humanized monoclonal antibody against the extracellular domain of HER-3/neu and Pegram et al. teach a successful method of treating a different epithelial cancer in a subject comprising administering to the subject a therapeutically effective amount of rhuMab HER2 which is also a humanized monoclonal antibody

against the extracellular domain of HER-3/neu, neither the art of record nor specification teach any anti-HER-2/neu antibody other than a humanized monoclonal antibody that binds specifically to the extracellular domain of HER-2/neu that is effective as a treatment for HER-2/neu overexpressing tumors.

Allegedly, one would not expect to be able to practice the claimed invention with an antibody that was not specific for the extracellular domain of HER-2/neu. For example, an antibody to the intracellular domain or an antibody that binds only to denatured HER-2/neu would not bind to malignant cells expressing ErbB-2, since the antibody could not contact the intracellular domain of the protein or would not be able to bind to an unfolded protein and therefore would not inhibit the cells growth and/or proliferation.

The Examiner further stated that as drawn to cross reactivity of the broadly claimed antibody, it is known in the art, as taught by Karunagaran et al. and Graus-Porta et al., that HER-2/neu is a member of the EGFR family and shares homology with other members of the family and therefore, given the shared homology it would be expected that antibodies that are not selective for HER-2/neu would cross react with, and be sequestered by, other members of the EGFR family.

The Examiner further stated that the claims as written read on not only monoclonal but also polyclonal antibodies. The Examiner stated that as set forth above, given the identity of HER-2/neu with other members of the EGFR family, it would be expected that a large majority of polyclonal antibodies would bind to epitopes that are shared among members of the EGFR family.

The Examiner further stated that as drawn to non-humanized antibodies for treatment of human subjects, which is clearly contemplated by the specification, Winter et al. specifically teach that a major problem with the use of murine monoclonal antibodies in the treatment of human subjects is the development of human antimouse antibodies (HAMA) that can inactivate the injected antibodies. The Examiner asserted that it would be expected that the injection of cross species antibody would result in anti-other species antibodies and/or cytotoxic T cells against the injected antibody. The Examiner stated that given the teaching in the art, it could not be predicted and it would not be expected that non-humanized antibodies would function as claimed, that is as therapeutics for the treatment of prostate cancer in human subjects.

The Examiner also stated that as drawn to treatment of prostate cancer that does not overexpress HER-2/neu, U.S. Patent No. 6,156,321 specifically teaches that among the drawbacks of antibody anti-tumor therapy is that antigen-negative cells can survive and repopulate a tumor (col. 1, line 64, col. 2, line 2). The Examiner stated that Lewis et al. specifically teach, in Table 2 in *in vitro* studies, that while proliferation of cell lines that overexpress ErbB2 was inhibited by treatment with anti-ErbB2 antibodies, proliferation of cell lines that do not overexpress ErbB2 was generally unaffected. Allegedly, no one of skill in the art would believe that it would be more likely than not that the invention would function as claimed in a prostate cancer that does not overexpress HER-2/neu.

The Examiner further stated that as drawn to treatment of prostate cancer regardless of the extent of expression of HER-2/neu, Pegram et al. specifically teach that Mab 4D5 and

Herceptin are known to have antiproliferative activity only against Her-2/neu-overexpressing human breast carcinoma cells *in vitro* and against *in vivo* animal models of breast cancer xenografts with HER-2/neu overexpression *in vivo*. The Examiner stated that it would not be expected and could not be predicted that successful Herceptin therapy could be used for the treatment of prostate cancers that did not overexpress HER-2/neu.

The Examiner concluded that the specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method will function as claimed with a reasonable expectation of success.

Again, applicants note that claim 30, not claim 29, was elected in response to the July 8, 2004 Restriction Requirement issued in connection with the subject application. Accordingly, applicants contend that a response to the rejection of claim 29 is not required and therefore, a response thereto has not been provided.

In addition, in response to the Examiner's rejection of claim 27, but without conceding the correctness thereof, applicants note that this claim has been cancelled without prejudice or disclaimer. Thus, the rejection thereof is moot.

In response to the Examiner's rejection of claim 19, applicants respectfully traverse, noting that amended claim 19 addresses the issues set forth above by the Examiner. Applicants contend that claim 19, as amended, satisfies the enablement requirement of 35 U.S.C. §112, first paragraph, and respectfully request that the

Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. §102(a)

The Examiner rejected claims 19 and 27-29 under 35 U.S.C. §102(a) as allegedly anticipated by Agus et al. (*supra*). The Examiner stated that Agus et al. teach a successful method of treating prostate cancer in a subject comprising administering to the subject a therapeutically effective amount of Herceptin, an anti-Her-2/neu antibody to the subject (abstract), the method further comprising administering an antitumor chemotherapeutic agent (see abstract), paclitaxel (see abstract), wherein the prostate cancer is androgen-dependent (see abstract). The Examiner stated that all of the limitations of the claims are met.

Again, applicants note that claim 30 (wherein the prostate cancer is androgen-independent), not claim 29, was elected in response to the July 8, 2004 Restriction Requirement issued in connection with the subject application. Accordingly, applicants contend that a response to the rejection of claim 29 is not required and therefore, a response thereto has not been provided.

In addition, in response to the Examiner's rejection of claim 27, applicants again note that claim 27 has been cancelled. Thus, the rejection thereof is moot.

In response to the rejection of claims 19 and 28, applicants respectfully traverse and maintain that Agus et al. is not prior art against the rejected claims. In support of their position, applicants submit a Declaration Under 37 C.F.R. §1.132 (**Exhibit A**). In this Declaration, inventor Dr. Carlos Cordon-Cardo declares that (a) he and co-inventor Dr. Howard I. Scher

conceived of the subject invention and are co-authors of Agus et al., and (b) the other co-authors of Agus et al. did not contribute to the conception of the invention as claimed. Therefore, Agus et al. is not prior art under 35 U.S.C. §102(a), since the invention was not "known or used *by others*...before the invention thereof by the applicant for patent." 35 U.S.C. §102(a).

In view of the above remarks, applicants maintain that claims 19 and 28 satisfy the requirements of 35 U.S.C. §102(a).

Claim Rejections Under 35 U.S.C. §103

Claims 19 and 29

The Examiner rejected claims 19 and 29 under 35 U.S.C. §103 as allegedly unpatentable over Baselga et al. in view of [Okumura et al.] Tokuda et al., Myers et al., Arai et al., Craft et al., and Zhau et al.

The Examiner stated that the claims are drawn to a method of treating prostate cancer in a subject comprising administering to the subject a therapeutically effective amount of anti-Her-2/neu antibody to the subject (claim 19), wherein the prostate cancer is androgen-dependent (claim 29).

The Examiner stated that Baselga et al. teach that Herceptin is well tolerated and clinically active in patients with HER-2 overexpressing metastatic breast cancers. The Examiner also stated that previous studies have demonstrated that the parent antibody, 4D5, is a potent inhibitor of growth, *in vitro*, and in xenograft models of human breast cancer cells that overexpress HER2. The Examiner asserted that Baselga et al. teach as set

forth above, but do not teach a method of treating prostate cancer with Herceptin.

The Examiner also stated that [Okumura et al.] Tokuda et al. teach the successful *in vivo* treatment of c-erbB-2 overexpressing human gastric carcinoma with Herceptin.

The Examiner further stated that Myers et al. teach that $p185^{erbB-2}$ is expressed on cell membranes of epithelial neoplastic lesions, from which prostatic adenocarcinoma appears to evolve, and on cell membranes of localized and metastatic adencoarcinomas. The Examiner stated that the frequently strong expression of $p185^{erbB-2}$ in both primary prostatic adenocarcinomas as well as matched nodal metastases from patients with stage D adenocarcinoma suggests that $p185^{erbB-2}$ may be used as a potential target in novel therapies.

The Examiner asserted that Arai et al. teach that approximately one third of clinically localized prostate cancers express c-erbB-2 and that Myers et al., *supra,* showed that increased expression of c-erbB-2 represents an early event in the development and progression of prostate cancer.

The Examiner also stated that Craft et al. teach that prostate cancer progresses from a hormone-sensitive, androgen-dependent stage to a hormone refractor, androgen-independent tumor and that radical prostectomy samples rarely contain androgen-independent disease and report varying frequencies of HER-2/neu overexpression and that most groups have focused on radical prostectomy samples.

The Examiner stated that Zhau et al. specifically teach the

observation of immunohistochemical staining of c-erbB-2/neu primarily around the plasma membranes of prostatic cancer cells.

The Examiner asserted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat the subset of patients with hormone-dependent prostate cancer that overexpress membrane HER-2/neu with the HER-2/neu specific antibody Herceptin of Baselga et al. and [Okumura et al.] Tokuda et al. The Examiner stated that Arai et al. and Myers et al. both specifically teach that HER-2/neu is overexpressed on at least a subset of prostate cancers and that Myers et al. specifically suggest that, given the identified frequently strong membrane expression of Her-2/neu in prostate cancer tumors, HER-2/neu may be used as a target in novel therapies for prostate cancer. The Examiner additionally stated that Baselga et al. specifically teach that Herceptin is well tolerated and clinically active in patients with epithelial HER-2 overexpressing tumors and that both *in vivo* and *in vitro* studies of the parent antibody, 4D5, have shown that this antibody is a potent inhibitor of growth of cancer cells. In addition, [Okumura] Tokuda et al. also teaches the successful treatment of a different type of epithelial tumor overexpressing HER-2 with Herceptin. The Examiner stated that one would have a reasonable expectation of success in treating the subset of patients with hormone-dependent prostate cancer that overexpresses membrane HER-2/neu with the HER-2/neu-specific antibody Herceptin of Baselga et al. and [Okumura et al] Tokuda et al. because prostate cancer is also an epithelial tumor that overexpresses HER-2/neu and Myers et al. and Zhau et al. specifically teach that expression of HER-2/neu is found at the cell membrane. Thus, it allegedly would be expected that the antibody would successfully target these tumor cells.

The Examiner stated that given the above, one would have had a reasonable expectation of success in treating prostate cancer with the known effective and well tolerated anti-HER-2/neu antibody. The Examiner also stated that it would have been *prima facie* obvious to one of ordinary skill in the art, and one would have been motivated, to specifically treat hormone-dependent prostate cancer in order to treat diagnosed cancer in an early stage at time of diagnosis. The Examiner stated that Craft et al. specifically teach that prostate cancer progresses from a hormone-dependent stage to a hormone-independent stage and that samples from radical prostectomy, generally done at time of diagnosis, rarely contain hormone-independent stage. The Examiner also stated that samples from radical prostectomy, generally done at time of diagnosis, rarely contain hormone-independent disease. The Examiner stated that Myers et al. teach that increased expression of c-erbB-2 represents an early event in the development and progression of prostate cancer and that this expression is frequently strong membrane expression. The Examiner further stated that Veltri et al. teaches that assay of radical prostectomy specimen revealed that 96 of 124 samples express HER-2/neu. Thus, one allegedly would expect to successfully treat hormone-dependent prostate cancer with Baselga's well tolerated and clinically active antibody against HER-2/neu in prostate cancer that frequently expresses HER-2/neu on tumor cell membrane.

In response to the Examiner's rejection, applicants respectfully traverse and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Again, applicants note that claim 30 (wherein the prostate cancer is androgen-independent), not claim 29, was elected in response

to the July 8, 2004 Restriction Requirement issued in connection with the subject application.

Claims 19, as amended, and 30 provide a method for treating a subject having prostate cancer comprising administering to the subject therapeutically effective amounts of (i) a humanized monoclonal antibody which specifically binds to an extracellular domain of the Her-2/neu protein and (ii) paclitaxel, wherein the prostate cancer is androgen-independent.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Applicants contend that the references cited against the rejected claims fail to support a *prima facie* case of obviousness, in that they would have failed to motivate one of skill in the art to combine them at the time of the invention.

Applicants maintain that the combination of the cited references does not render the claimed invention obvious because the combined teaching would not have lead one of ordinary skill in the art to reasonably expect that an anti-Her-2/neu antibody could be used to treat androgen-independent prostate cancer. In fact, the art teaches away from the use of an anti-Her-2/neu antibody to treat androgen-independent prostate cancer. As the Examiner pointed out above, Craft et al. teach that samples from radical prostectomy, generally done at the time of diagnosis,

rarely contain androgen-independent prostate cancer. The Examiner also pointed out that Myers et al. teach that increased expression of c-erbB-2 represents an early event in development and progression of prostate cancer, which according to Craft et al. is associated with androgen-dependent prostate cancer. For that reason, one of skill in the art would not expect increased expression of Her-2/neu in androgen-independent prostate cancer. Therefore, applicants maintain that the need to combine an anti-Her-2/neu antibody and an antitumor chemotherapeutic agent such as paclitaxel could not be suggested by the references. Accordingly, the cited references cannot be said to render the claimed invention obvious because there was no reasonable expectation of success in performing the claimed method for treating androgen-independent prostate cancer using a combination of an anti-Her-2/neu antibody and an antitumor chemotherapeutic agent such as paclitaxel.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 19 and 30 over these references.

In view of the above remarks, applicants maintain that claims 19 and 30 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims 19 and 27-28

The Examiner rejected claims 19 and 27-28 under 35 U.S.C. §103 as allegedly unpatentable over Baselga et al. in view of [Okumura et al.] Tokuda et al., Myers et al., Arai et al., Craft et al., Zhau et al., above and further in view of Shaw et al.

The Examiner stated that the claims are drawn to a method of

treating prostate cancer in a subject comprising administering to the subject a therapeutically effective amount of anti-Her-2/neu antibody to the subject (claim 19), the method further comprising administering an antitumor chemotherapeutic agent (claim 27), paclitaxel (claim 28).

The Examiner stated that the references of the prior art teach as set forth above but do not teach combination therapy comprising Herceptin combined with paclitaxel.

The Examiner stated that Shaw et al. teach the successful treatment of subjects having prostate cancer with paclitaxel.

The Examiner asserts that it would have been *prima facie* obvious to include the paclitaxel of Shaw et al. in the method of the combined prior art references because Shaw specifically teaches the successful treatment of subjects with prostate cancer with paclitaxel.

The Examiner stated that since paclitaxel had been taught by the prior art to be effective in the treatment of prostate cancer and it would be expected, for the reasons set forth above that Herceptin would successfully treat prostate cancer, the instant situation is amenable to the type of analysis set forth *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980). According to the Examiner, in this case, the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to make a third composition that is used for the very same purpose since the idea of combining them flows logically from their having been individually taught in prior art. The Examiner stated that applying the same logic to the instant claims, given the teaching

of the prior art that paclitaxel is effective in treating prostate cancer, it would have been obvious to treat cancer with both the Herceptin of the combined prior art references and paclitaxel because the idea of doing so would have logically followed from their having been individually taught to be useful as cytotoxic agents for the same purpose, treating prostate cancer. The Examiner stated that one of ordinary skill in the art would have reasonably expected to treat prostate cancer with either or both of these agents since both the Herceptin of the combined references and the paclitaxel of Shaw et al. had been demonstrated to kill tumors.

In response to the Examiner's rejection, applicants respectfully traverse and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

In response to the Examiner's rejection of claim 27, applicants again note that this rejection is moot in view of the claim's cancellation.

Claims 19, as amended, and 28 provide a method for treating a subject having prostate cancer comprising administering to the subject therapeutically effective amounts of (i) a humanized monoclonal antibody which specifically binds to an extracellular domain of the Her-2/neu protein and (ii) paclitaxel.

Applicants contend that the references cited against the rejected claims fail to support a *prima facie* case of obviousness, in that they fail to create a reasonable expectation of success.

Without experimentation, one of ordinary skill cannot reasonably predict that a successful anti-cancer outcome will occur using a

particular combination of two drugs, even though each drug, when used individually, has anti-cancer effects. For example, in studies of patients with stage IV renal cell cancer, researchers have found that attempts to combine known renal cancer fighting drugs, i.e. Proleukin and alfa interferon, have been unsuccessful (see page 3 of **Exhibit B** which is attached hereto). In other words, each specific combination of two or more anti-cancer agents must be tested before one of skill in the art can know that such combination will be effective against cancer, let alone more effective than either agent alone. The Examiner has failed to show otherwise.

Underscoring the unpredictability of success when combining two anti-cancer agents is U.S. Patent No. 5,597,830 (attached hereto as **Exhibit C**), wherein the inventors demonstrate that there are limitations to combination therapy and that anti-cancer agents such as taxol and other taxanes are actually *inhibited* by the oncolytic agent Suramin (see col. 4; Figure 3; and Figure 6).

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 19 and 28 over these references.

In view of the above remarks, applicants maintain that claims 19 and 28 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and earnestly solicit allowance of the

pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $510.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
Tel. No. (212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

8/3/01

Alan J. Morrison Date
Reg. No. 37,399